Pharmacia & Upjohn

GLOBAL SUPPLY--ACTIVE PHARMACEUTICAL INGREDIENTS
REGULATORY

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: **Docket Number 980-0994**; Guidance for Industry, BACPAC I: Intermediates in Drug Substance Synthesis, Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation.

Dear Sir/Madam:

Pharmacia & Upjohn endorses the spirit, philosophy, and content of BACPAC I. We believe this represents a significant step towards relieving industry of the regulatory burdens associated with scientifically justifiable postapproval changes to API registrations. Nevertheless, we wish to provide a series of comments that we believe are worthy of consideration for modifying the draft guidance.

1. In the Introduction, lines 15-16, it is stated that specification changes to the final intermediate are not covered by BACPAC I. Since site, scale, equipment, and processing changes including the step that produces the final intermediate are included in BACPAC I, we believe that specification changes to the final intermediate should also be covered because analytical changes covered by BACPAC I are typically what drives the specifications for a final intermediate.
2. Within the Introduction section, lines 32-39, reference is made to 21 CFR 314.70 for changes to approved applications and that BACPAC I addresses certain postapproval changes within the meaning of 21 CFR 314.70. Clarity would be added if line 36 were modified to read ... "burdensome notice of certain postapproval changes to approved applications within the meaning of 21 CFR 314.70(a) and changes to existing master files supporting approved applications within the meaning of 21 CFR 314.420." Such a statement clarifies that BACPAC I only applies to information and processing described within existing registration documents.

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3. In lines 88-91, we suggest the following rewording: "However, the stability of some drug products may be affected by small changes in drug substance impurities (e.g. in trace levels of heavy metals). For such drug products, a commercial batch of drug product made with postchange drug substance should be included in the firm's stability testing program."
4. Also, in lines 95-97, the discussion states for a drug substance that is a mixture of isomers, demonstration of equivalence after changes to the manufacturing process includes showing that the mixture of isomers in the drug substance is quantitatively the same. First, we believe that isomeric equivalence could also be demonstrated with intermediates including the final intermediate. Second, the situation in which an isomer/diasterioisomer is considered an impurity and a process change is directed towards decreasing the level of this impurity would not be able to meet the test of isomeric equivalence. We suggest the following wording beginning on line 94: "However, other factors that may be important in individual cases, e.g. chirality, should be evaluated to demonstrate equivalence. There should be no structural changes to the final intermediate or to the drug substance."
5. We have a general comment relative to the requirement within BACPAC I to submit as part of the test documentation the validation data for new or extended test methods, certificates of analysis for raw materials, solvents, or intermediates, and protocols establishing change control practices for new suppliers. This is information not typically included or detailed in an original filing, but is available for field investigators to review during PAI or routine GMP inspections. The detail and scope of a submission for a postapproval change should be consistent with that currently required for primary registrations. We suggest that BACPAC I wording be modified such that submission of certificates of analysis and change control protocols not be required and that a brief summary of new or modified analytical methods and validation results is sufficient to support a change.
6. We also comment that in establishing prechange or historical limits for comparison to postchange results, some flexibility should be allowed for postapproval changes where the drug substance comes from a low volume manufacturing activity or is associated with a recently approved application and where an extensive commercial scale database may not be available. First, we believe that it should be acceptable to include pilot scale or development scale data within the historical database so long as these alternate scales mimic or adequately reflect the commercial scale process. Second, in those situations in which a statistical limit is not appropriate or is illogical, comparison of the post-change results to established or registered limits should be acceptable to demonstrate equivalence.

We have a major comment regarding the manner in which BACPAC I addresses process changes compared to other types of change. BACPAC I provides the flexibility of using annual reporting (AR) for filing documentation where equivalence can be demonstrated before and after certain changes of site, scale, equipment, and specifications. If equivalence before and after a change is demonstrable for a manufacturing process change, BACPAC I should allow the same filing options offered for other types of change.

- For process changes that do not involve new starting materials or intermediates, an AR should be allowed where equivalence can be demonstrated prior to the API. If equivalence can only be shown at the API stage a Changes Being Effected (CBE) filing would be appropriate.
- For changes in the route of synthesis in one or more steps involving different starting materials and/or intermediates, an AR should be acceptable for early steps and intermediates in lengthy multistep processes. A CBE submission would apply to late intermediates (steps proximal to the final intermediate in lengthy multistep processes), and a prior approval submission (PAS) would be necessary where the final intermediate is involved or equivalence can only be demonstrated at the API stage.
- For changes where an early intermediate is redefined as a starting material, an AR is appropriate. Such changes associated with late intermediates or where equivalence can only be shown at the API would require a CBE submission.

Since FDA is willing to confer with registration holders to define when a CBE is appropriate instead of a PAS, a similar conference mechanism for discerning AR versus CBE submissions should be provided. This would address whether changes early in a processing sequence qualify for annual reporting.

7. We also have a major comment regarding how BACPAC I addresses regulatory relief for master file holders. Although BACPAC I provides considerable filing relief and flexibility to holders of NDA's, ANDA's, NADA's, and ANADA's, the only mechanism available to the DMF or VMF holder is filing an amendment. We believe for example, if the change to be implemented by a DMF holder is reportable by the NDA holder(s) as an annual report(s), it should be acceptable for the DMF holder to submit the change as an annual update to the DMF. Use of annual updates for DMF and VMF holders for changes of this nature allows more timely implementation of scientifically justified changes that the approved application holder(s) supports; however, it does not tie the DMF or VMF holder's submission to the timing of the sponsors' annual report(s). Allowing this flexibility has no impact on FDA's review accountabilities, but provides significant regulatory relief to DMF and VMF holders.

Pharmacia & Upjohn strongly supports the philosophy and content of BACPAC I and applauds FDA's actions in developing this draft guidance. We ask that FDA earnestly consider our comments and those from others in industry in order to best address postapproval changes.

Sincerely yours,

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